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(54) Title: AMINE SALTS OF (-)-2-((2-(4-HYDROXYPHENYL)ETHYL)THIO)-3-(4-(2-(4-((METHYLSULFONYL)OXY) PHENOXY)ETHYL)PHENYL) PROPANOIC ACID

(57) Abstract: A cinchonidine salt, an (R)-(+)-1-(1-naphthyl)ethylamine salt and a (S)-(-)-1-(2-naphthyl)ethylamine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid, processes for their preparation, their use in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, and pharmaceutical compositions containing them.

AMINE SALTS OF (-)-2-((2-(4-HYDROXYPHENYL)ETHYL)THIO)-3-(4-(2-(4-((METHYLSULFONYL)OXY)PHENOXY)ETHYL)PHENYL)PROPANOIC ACID

Field of the invention

The present invention relates to a cinchonidine salt, an (R)-(+)-1-(1-naphthyl)ethylamine salt and a (S)-(-)-1-(2-naphthyl)ethylamine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-propanoic acid to processes for their preparation, to their use in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, and to pharmaceutical compositions containing them.

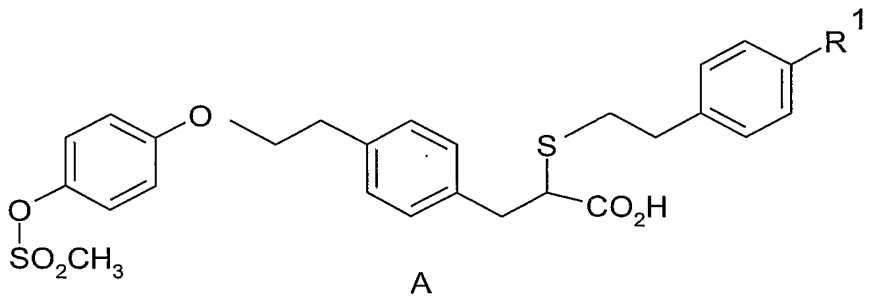
Background of the invention

The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in patients with the metabolic syndrome and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

Co-pending PCT application No. PCT/GB02/05743 (WO 03/051826) discloses compounds of formula A



A

wherein R^1 represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof which are selective PPARα modulators (for a review of the PPARs (peroxisome proliferator-activated receptors) see T. M.Willson et al , J Med Chem 2000, Vol 43, 527). These compounds are effective in treating conditions associated with insulin resistance. Specific pharmaceutically-acceptable salts of compounds of the formula A are not disclosed in PCT/GB02/05743. The (-) enantiomer of the compound in which R^1 represents hydroxy is prepared as the free acid in this application. However, this compound is a thick oil with a syrup-like consistency and thus is not suitable for use in pharmaceutical formulations. Co-pending PCT WO2004113283 discloses certain amine salts of this acid and co-pending PCT WO2004113284 discloses certain metal salts of this acid. There is still a need for alternative solid forms of this compound that have physical and chemical properties suitable for use in pharmaceutical formulations. Many salts were tried but most of these either could not be formed in the solid state or were amorphous with a low glass transition temperature. Salts with suitable properties for pharmaceutical formulation have now been found.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should preferably be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also important to be able to provide the drug in a form which is as chemically pure as possible.

The skilled person will appreciate that, typically, if a drug can be readily obtained in a stable form, such as a stable crystalline form, advantages may be provided, in terms of ease of handling, ease of preparation of suitable pharmaceutical formulations, and a more reliable solubility profile.

Description of the invention

The present invention provides a cinchonidine salt, an (R)-(+)-1-(1-naphthyl)ethylamine salt and a (S)-(-)-1-(2-naphthyl)ethylamine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-propanoic acid.

It will be understood that the present invention includes one or any combination of more than one of the above salts.

We have found that certain compounds of the invention have the advantage that they may be prepared in crystalline form.

According to a further aspect of the invention there is provided a compound of the invention in substantially crystalline form.

Although we have found that it is possible to produce compounds of the invention in forms which are greater than 80% crystalline, by "substantially crystalline" we include greater than 20%, preferably greater than 30%, and more preferably greater than 40% (e.g. greater than any of 50, 60, 70, 80 or 90%) crystalline.

According to a further aspect of the invention there is also provided a compound of the invention in partially crystalline form. By "partially crystalline" we include 5% or between 5% and 20% crystalline.

The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR,

Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used.

Compounds of the invention, and particularly crystalline compounds of the invention, may have improved stability when compared to compounds disclosed in PCT/GB02/05743.

The term "stability" as defined herein includes chemical stability and solid state stability.

By "chemical stability", we include that it may be possible to store compounds of the invention in an isolated form, or in the form of a formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

By "solid state stability", we include that it may be possible to store compounds of the invention in an isolated solid form, or in the form of a solid formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, recrystallisation, solid state phase transition, hydration, dehydration, solvatisation or desolvatisation).

Examples of "normal storage conditions" include temperatures of between minus 80 and plus 50°C (preferably between 0 and 40°C and more preferably room temperatures, such as 15 to 30°C), pressures of between 0.1 and 2 bars (preferably at atmospheric pressure), relative humidities of between 5 and 95% (preferably 10 to 60%), and/or exposure to 460 lux of UV/visible light, for prolonged periods (i.e. greater than or equal to six months). Under such conditions, compounds of the invention may be found to be less than 15%, more preferably less than 10%, and especially less than 5%, chemically degraded/decomposed, or solid state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature, pressure and relative humidity represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).

It may be possible to crystallise salts of compounds of the present invention with or without the presence of a solvent system (e.g. crystallisation may be from a melt, under supercritical conditions, or achieved by sublimation). However, we prefer that crystallisation occurs from an appropriate solvent system.

According to a further aspect of the invention, there is provided a process for the preparation of a crystalline compound of the invention which comprises crystallising a compound of the invention from an appropriate solvent system.

Crystallisation temperatures and crystallisation times depend upon the salt that is to be crystallised, the concentration of that salt in solution, and the solvent system that is used.

Crystallisation may also be initiated and/or effected by way of standard techniques, for example with or without seeding with crystals of the appropriate crystalline compound of the invention.

Different crystalline forms of the compounds of the invention may be readily characterised using X-ray powder diffraction (XRPD) methods, for example as described hereinafter.

In order to ensure that a particular crystalline form is prepared in the absence of other crystalline forms, crystallisations are preferably carried out by seeding with nuclei and/or seed crystals of the desired crystalline form in substantially complete absence of nuclei and/or seed crystals of other crystalline forms. Seed crystals of appropriate compound may be prepared, for example, by way of slow evaporation of solvent from a portion of solution of appropriate salt.

Compounds of the invention may be isolated using techniques which are well known to those skilled in the art, for example decanting, filtering or centrifuging.

Compounds may be dried using standard techniques.

Further purification of compounds of the invention may be effected using techniques, which are well known to those skilled in the art. For example impurities may be removed by way of recrystallisation from an appropriate solvent system. Suitable temperatures and times for the recrystallisation depend upon the concentration of the salt in solution, and upon the solvent system that is used.

When compounds of the invention are crystallised, or recrystallised, as described herein, the resultant salt may be in a form which has improved chemical and/or solid state stability, as mentioned hereinbefore.

Compounds of the invention have the advantage that they are highly crystalline and easy to handle during processing. They are also capable of providing large crystals which can be used in determinations of absolute stereochemistry. The salts are also useful in purifying the acid from impurities by crystallisation prior to conversion back to the free acid and/or conversion into another salt.

Compounds of the invention have the advantage that they may be more efficacious, be less toxic, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, be more easily absorbed, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance), than, and/or have other useful pharmacological, physical, or chemical, properties over, compounds known in the prior art. Compounds of the invention may have the further advantage that they may be administered less frequently than compounds known in the prior art.

Compounds of the invention may also have the advantage that they are in a form which provides for improved ease of handling. Further, compounds of the invention have the advantage that they may be produced in forms that may have improved chemical and/or solid state stability (including e.g. due to lower hygroscopicity). Thus, such compounds of the invention may be stable when stored over prolonged periods.

Compounds of the invention may also have the advantage that they may be crystallised in good yields, in a high purity, rapidly, conveniently, and at a low cost.

These salts have activity as medicaments, in particular the salts are selective agonists of PPARα, that is, their EC_{50} for PPARα is at least ten times lower than their EC_{50} for PPARγ wherein the EC_{50}s are measured and calculated as described in the assays later in this document. The compounds are potent and selective.

It will be understood by those skilled in the art that where (-) occurs in this specification that the acid has a negative rotation when measured using the conditions and concentration described in the experimental section. It should be understood that the salts of the present invention may have (+) rotation provided that the absolute configuration of the salt is the same as the configuration of the (-)-parent acid.

It will also be understood that the compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated and unsolvated forms.

Methods of preparation

The compound of the invention may be prepared as outlined below. However, the invention is not limited to these methods.

The salts may be prepared by reacting (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid with the appropriate amine, for example cinchonidine, (R)-(+)-1-(1-naphthyl)ethylamine or (S)-(-)-1-(2-naphthyl)ethylamine in an inert solvent, for example ethanol, methanol, propan-2-ol, ethyl acetate, toluene or mixtures thereof or a mixture of ethanol or methanol or propan-2-ol and water, at a temperature in the range of 0-100°C and isolating the solid salt. The salt may be isolated by cooling the reaction solution and optionally seeding the solution with the desired product and/or concentrating the solution. Optionally the product may be isolated by adding an antisolvent to a solution of the product in an inert solvent. The solid may be collected by methods known to those skilled in the art for example filtration or centrifugation.

(-)-2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid may be prepared as described in WO 03/051826.

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

In another aspect the present invention provides the compound obtainable by reacting (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl) phenyl] propanoic acid and cinchonidine in ethanol and isolating the product.

In another aspect the present invention provides the compound obtainable by reacting (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid and (R)-(+)-1-(1-naphthyl)ethylamine in ethanol and isolating the product.

In another aspect the present invention provides the compound obtainable by reacting (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid and (S)-(-)-1-(2-naphthyl)ethylamine in ethanol and isolating the product.

Particularly an equivalent of the amine is used or an equivalent plus a slight excess of amine.

Pharmaceutical preparations

A compound of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including the compound of the invention in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

A compound of the invention is useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein

(VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

A compound of the present invention is expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome.

Treatment with a compound of the present invention is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of its insulin sensitizing effect the compound iss also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore a compound of the present invention may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

A compound of the present invention is expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of the present invention to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of the present invention to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of the present invention as a medicament.

In a further aspect the present invention provides the use of a compound of the present invention in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

Combination Therapy

A compound of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. A compound of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus a compound of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

A compound of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt thereof, may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and/or delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, WO 04/000790, WO 04/000295, WO 04/000294, WO 03/051822, WO 03/051821, WO 02/096863, WO 03/051826, WO 02/085844, WO 01/040172, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the

patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma and/or delta agonist refers to muraglitazar (BMS 298585), rivoglitazone (CS-011), netoglitazone (MCC-555), balaglitazone (DRF-2593, NN-2344), clofibrate, fenofibrate, bezafibrate, gemfibrozil , ciprofibrate, pioglitazone, rosiglitazone, AVE-0847, AVE-8134, CLX-0921, DRF-10945, DRF-4832, LY-518674, LY-818, LY-929, 641597, GW-590735, GW-677954, GW-501516, MBX-102, ONO-5129, KRP-101, R-483 (BM131258), TAK-559 or TAK-654. Particularly a PPAR alpha and/or gamma and/or delta agonist refers to tesaglitazar ((S)-2-ethoxy-3-[4-(2-{4-methanesulphonyl-oxyphenyl}ethoxy)phenyl]-propanoic acid) and pharmaceutically acceptable salts thereof.

In addition a compound of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcylamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. The present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this combination section. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly

preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[*N*-methyl-*N*-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and EP624596 and the contents of these patent applications are incorporated herein by reference.

Further suitable compunds possessing IBAT inhibitory activity have been described in WO 94/24087, WO 98/56757, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 02/08211, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, WO 03/091232, WO 03/106482, JP

10072371, US 5070103, EP 251 315, EP 417 725, EP 869 121, EP 1 070 703 and EP 597 107 and the contents of these patent applications are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols;

probucol;

an omega-3 fatty acid for example Omacor^{TM};

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker for example metoprolol, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;

aspirin;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of the present invention include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of the present invention include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the present invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the present invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the present invention, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of the present invention and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of the present invention in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of the present invention together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the present invention of the present invention and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the present invention and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Experimental

^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Example 1

(-)-2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid L-(-)-cinchonidine salt

(-)-2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid (1.2g) was dissolved in ethanol (6ml). L-(-)-cinchonidine (0.68g) was added and the mixture warmed to give a clear solution. The solution was stirred and seeded with the title compound. The title compound crystallised as a colourless solid. Stirring was continued at room temperature for 2.5 hours and then the product was collected by filtration to give the title compound 1.47g m.p.139-140°C. This salt appeared to be highly crystalline under the microscope. ^{1}H nmr confirmed the structure.

Example 2

(-)-2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid (R)-(+)-1-(1-naphthyl)ethylamine salt

(-)-2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid (1.34g) was dissolved in ethanol (13.7ml). (R)-(+)-1-(1-naphthyl)ethylamine (0.43ml) was added to give a pale yellow solution. The volume was reduced by rotary evaporation to approximately 5ml during which a solid was formed. A sample of this solid appeared to be amorphous under the microscope and so the mixture was re-heated to give a clear solution and seeded with title compound. The title compound precipitated. A sample of this solid appeared to be mainly amorphous but with some crystals under the microscope. The mixture was stirred at room temperature for 3 days. Examination of a sample showed that the solid was totally crystalline. The product was collected by filtration, washed with ethanol and dried on the filter. On drying under vacuum at 50°C the compound melted and so was re-dissolved in ethanol, seeded with the title compound and stirred overnight. The product was collected by filtration and dried at room temperature to give the title compound 0.67g m.p.98-102°C. This salt appeared to be highly crystalline under the microscope. ^{1}H nmr confirmed the structure.

Example 3

(-)-2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid (S)-(-)-1-(2-naphthyl)ethylamine salt

(-)-2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid (1.09g) was dissolved in ethanol (6ml). (S)-(-)-1-(2-naphthyl)ethylamine (0.36g) was added to give a clear solution. The solution was stirred overnight at room temperature. The mixture set solid. A sample of this solid appeared to be a mixture of amorphous and crystalline material under the microscope. More ethanol (4ml) was added and the mixture was warmed to give a clear solution and then cooled. The solid formed was amorphous and so the mixture was warmed to 50°C with stirring. On continued stirring crystalline material was formed. A further 2ml of ethanol was added to facilitate stirring and the mixture was stirred at 51°C for 1 hour. The mixture was cooled to 40°C and the product was collected by filtration and dried at room temperature to give the title compound 0.95g m.p.121-122°C. This salt appeared to be highly crystalline under the microscope. ^{1}H nmr confirmed the structure.

CLAIMS

1. A compound selected from:

a cinchonidine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid,

an (R)-(+)-1-(1-naphthyl)ethylamine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid and

a (S)-(-)-1-(2-naphthyl)ethylamine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid.

2. The cinchonidine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid.

3. The (R)-(+)-1-(1-naphthyl)ethylamine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid.

4. The (S)-(-)-1-(2-naphthyl)ethylamine salt of (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid.

5. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 4 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

6. A method of treating or preventing lipid disorders (dyslipidemia) whether or not associated with insulin resistance comprising the administration of a compound according to any one of claims 1 to 4 to a mammal in need thereof.

7. The use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment of lipid disorders (dyslipidemia) whether or not associated with insulin resistance.

8. A method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound according to any one of claims 1 to 5 to a mammal in need thereof.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity.

10. A method of preparing a salt according to claim 1 comprising reacting (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-propanoic acid with an appropriate amine, selected from cinchonidine, (R)-(+)-1-(1-naphthyl)ethylamine or (S)-(-)-1-(2-naphthyl)ethylamine in an inert solvent at a temperature in the range of 0-100°C and isolating the solid salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/004829

A. CLASSIFICATION OF SUBJECT MATTER
C07C323/56 A61K31/192 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/051826 A (ASTRAZENECA) 26 June 2003 (2003-06-26) cited in the application page 6, lines 7-9; claims 1,4,6,8-10,14; example 2	1-10
P,A	WO 2004/113283 A (ASTRAZENECA) 29 December 2004 (2004-12-29) cited in the application claims 1,10-14	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2006	17/03/2006

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/004829

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6,8 directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/004829

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03051826 A	26-06-2003	AU 2002352426 A1	30-06-2003
		BR 0215090 A	16-11-2004
		CA 2470066 A1	26-06-2003
		CN 1620430 A	25-05-2005
		EP 1458677 A1	22-09-2004
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		US 2005215630 A1	29-09-2005
WO 2004113283 A	29-12-2004	AU 2004249483 A1	29-12-2004
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